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Original Article

Twenty-one years of prospective incidence of childhood type 1 diabetes in Hungary – the rising trend continues (or peaks and highlands?)

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The aim of this study was to examine secular trends in the incidence of type 1 diabetes in children aged 0–14 yr in Hungary over the period 1989–2009. Newly diagnosed children with type 1 diabetes aged 0–14 yr in Hungary were prospectively registered from 1989 to 2009. Primary ascertainment of cases was by prospective registration using hospital notifications. Case ascertainment was over 96% complete using the capture–recapture method. Standardized incidence rates were calculated and secular trends estimated using Poisson regression analysis. In Hungary during 1989–2009 a total number of 3432 children were identified, giving a standardized incidence rate of 12.5 [95% confidence interval (CI) 12.1–12.9] per 100 000 person yr. The overall incidence rate has doubled from 7.7 (95% CI 6.4–9.15) per 100 000 per yr in 1989 to 18.2 (95% CI 15.7–20.9) per 100 000 per yr in 2009. A significant linear trend in incidence ($p < 0.001$) has been observed over time, with a mean annual increase of 4.4%. The increase in incidence was present in both genders and in all age groups, with the largest relative increase in the youngest age group (6.2%; $p < 0.001$). The incidence of type 1 diabetes in Hungarian children continues to increase, with the highest rate in the very young. Although it seems that transient periods of stabilization followed by increases in incidence are apparent, the long-term trend continues to be steadily upward. Incidence of childhood type 1 diabetes is a dynamic process, probably reflecting the changes of the environmental exposures and continued registration is necessary to recognize these trends.

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Apart from the extremely wide global variation in incidence, there were two major characteristics of the epidemiology of childhood type 1 diabetes over the last few decades of the twentieth century. Incidence increased in most countries (1) and this trend was accompanied by a shift in the age of onset to the youngest age group (0–4 yr) (2). Recent observations from Sweden, a country with a very high incidence rate, suggest that, contrary to analyses in most other countries, there are indications of declining rates in the youngest children in recent years, in particular among those born after the year 2000 (3).

Our analysis of the most recent incidence data (up to the year of 2009) for a central European country with a medium incidence demonstrates a long-term overall increasing incidence trend and argues that the brief periods of apparent stabilization of rates (that have been seen in our registry and have been reported by others before) are probably transient and the general trend continues to be upward.

Study design

The area of Hungary is divided into 19 counties, of which 18 were included. Budapest, the capital, and the surrounding region were excluded from our study because historically we have found that the ascertainment level was low (4). There are several pediatric departments in the capital, and some of them – particularly in the first years of the registry – were unable to provide reliable case data. The children's population of Budapest is about one fourth of national total. The Hungarian population aged 0–14 yr in 18 counties decreased by one third from 1 579 450 (1989) to 1 052 184 (2009) during the study period.

In Hungary, prospective registration as part of the EURODIAB study started in 1989 (1). The establishment of the Hungarian Childhood Diabetes Register has previously been described in detail (4). Children with newly diagnosed type 1 diabetes under the age of 15 yr are prospectively registered. All cases diagnosed between 1 January 1989 and 31 December 2009 were included in the analysis. In Hungary, children with new-onset diabetes aged 0–14 yr are hospitalized in pediatric departments at the time of diagnosis. Hospital case records served as the primary source and we used the list of children who attended diabetes summer camps as an independent secondary source of ascertainment. These camps, organized by trade unions and later by charity organizations, were open to all diabetic children. Capture–recapture method was used to estimate the completeness of case registration (5). All denominators for incidence calculations were provided annually by the Central Bureau of Statistics.

Statistical methods

Annual end-year population estimates were used as denominators for calculation of rates. Age- and sex-standardized incidence rates were obtained using the direct method with a standard population consisting of equal numbers of children in each of the six subgroups defined by age group (0–4 yr, 5–9 yr, and 10–14 yr) and gender. Confidence intervals (CIs) for rates were calculated assuming that the observed number of cases followed a Poisson distribution. Poisson regression models were used to assess time trends in incidence. Models with terms for age group, gender, and calendar year were fitted. Interactions were fitted to assess if the trends differed significantly between age groups or genders.

Predictions for future new cases until 2030 were made by extrapolating rates using the annual percentage increase in incidence in each age/sex subgroup estimated from the Poisson regression model.

Results

The average standardized incidence rate

A total of 3432 patients (1777 boys and 1655 girls) under the age of 15 yr were registered during the observation period. Ascertainment was above >95% throughout the 21-yr period with a uniform pattern over time: 1989–1993, 97.9%; 1994–1998, 95.9%; 1999–2003, 97.5%; and 2004–2009, 100%.

The average standardized incidence rate was 12.5 (95% CI 12.0–12.9) per 100 000 per annum over the 21 yr, 12.6 (95% CI 12.0–13.2) in boys, and 12.3 (95% CI 11.72–12.9) in girls. The age-specific incidence rates were 8.8 (95% CI 8.2–9.5), 13.5 (95% CI 12.7–14.3), and 15.1 (95% CI 14.3–15.8) per 100 000 person yr in the 0–4, 5–9, and 10–14-yr age groups, respectively.

Incidence trend

The incidence increased from 7.7 (95% CI 6.3–9.0) per 100 000 person yr in 1989 to 18.2 (95% CI 15.7–20.9) in 2009 (Fig. 1). Table 1 shows the mean age- and sex-specific incidence rates by three 5-yr and one 6-yr periods. The increase in incidence rate for the entire cohort (and in both sexes and in all three age groups) was highest between the periods 1999–2003 and 2004–2009.

Results of the Poisson regression analysis are summarized in Table 2. This analysis demonstrated a highly significant linear trend in incidence over the 21-yr period (line 1, Table 2). Fitting of a quadratic term in year showed no evidence of significant departure from linearity in the secular trend (line 2, Table 2). Interestingly, year 2004 is an outlier with its unusually high incidence rate and 95% CIs above the estimated trendline, although rates for the years 2005 and 2006 are also above the linear prediction (Fig. 1). There was also evidence of a significant difference in the trends between age groups (line 3, Table 2) and between genders (line 4, Table 2) with rates increasing faster in the younger age groups and in boys. However,

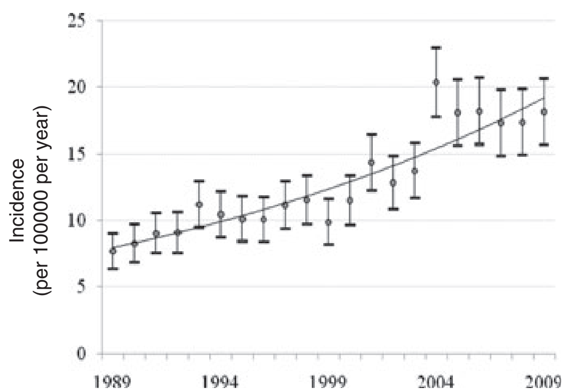

Fig. 1. Age-standardized incidence rate (with 95% confidence intervals) for type 1 diabetes in children aged 0–14 yr in Hungary for each year in the period 1989–2009 with fitted log-linear trend.

Table 1. Age- and sex-specific incidence rates of type 1 diabetes in Hungary during 1989–2009; incidence per 100 000 per yr (95% confidence interval) by three 5-yr and a 6-yr periods

	1989–1993	1994–1998	1999–2003	2004–2009
Boys				
0–4	5.1 (3.8–6.4)	8.0 (6.3–9.7)	8.3 (6.4–10.1)	14.3 (12.0–16.6)
5–9	9.7 (7.9–11.4)	10.4 (8.5–12.2)	12.7 (10.6–14.9)	21.1 (18.4–23.8)
10–14	11.5 (9.8–13.3)	12.4 (10.4–14.4)	16.6 (14.3–18.9)	22.4 (19.8–25.0)
Girls				
0–4	5.4 (4.0–6.7)	7.2 (5.5–8.8)	9.5 (7.5–11.6)	13.8 (11.5–16.1)
5–9	9.4 (7.6–11.2)	12.1 (10.1–14.2)	13.8 (11.6–16.1)	19.9 (17.2–22.6)
10–14	13.0 (11.1–14.9)	13.9 (11.7–16.0)	13.5 (11.4–15.7)	17.7 (15.5–20.1)
Boys and girls				
0–4	5.2 (4.3–6.3)	7.6 (6.5–8.9)	8.9 (7.5–10.3)	14.1 (12.6–15.9)
5–9	9.5 (8.3–10.8)	11.3 (9.9–12.7)	13.3 (11.8–14.9)	20.5 (18.6–22.5)
10–14	12.3 (11.0–13.6)	13.1 (11.7–14.6)	15.1 (13.6–16.8)	20.1 (18.3–21.8)
Stand incidence	9.0 (8.4–9.7)	10.6 (9.9–11.5)	12.4 (11.6–13.3)	18.3 (17.3–19.4)

Table 2. Summary of Poisson regression analyses fitted to data in 3 age groups, 2 sexes, and 21 yr

			Likelihood ratio test on last model term			Goodness-of-fit test		
	Model	−2 log L	χ^2	df	p	χ^2	df	p
0	A+S+A•S	1020.37				381.97	120	<0.001
1	A+S+A•S+Y	784.34	236.04	1	<0.001	145.93	119	0.05
2	A+S+A•S+Y+Y^2	784.23	0.11	1	0.74	145.82	118	0.04
3	A+S+A•S+Y+Y•A	769.19	15.14	2	0.001	130.79	115	0.15
4	A+S+A•S+Y+Y•A+Y•S	763.37	5.82	1	0.016	124.97	116	0.27
5	A+S+A•S+Y+Y•A+Y•S+Y•A•S	760.36	3.01	2	0.22	121.96	114	0.29

A, age; S, sex; Y, linear term in year; Y^2, quadratic term in year; Y•A, interaction between Y and A.

the test for interaction (line 5, Table 2) did not detect any significant difference between boys and girls in the patterns of increase by age group.

Table 3 shows that there was an average annual increase of 4.4% (95% CI 3.9–5.0; $p < 0.001$) after adjustment for age and sex. Figure 2 shows that the increase was evident in both genders with higher rates for boys (5.1%; 95% CI 4.3–5.9; $p < 0.001$) compared with girls (3.7%; 95% CI 2.9–4.6; $p < 0.001$).

Boys showed faster rates of increase in incidence of type 1 diabetes in all three age groups than did girls, but only in the oldest age group was this difference significant ($p = 0.004$) (Table 3).

Incidence prediction

Assuming that the rates of increase observed in 1989–2008 continue, by 2030 the number of newly diagnosed children aged 0–14 yr in Hungary is predicted to be 2460 with a distribution of 31% being in the 0–4 yr, 38% in the 5–9 yr, and 31% in the 10–14-yr age groups. The predicted age-specific incidence rates are, respectively, 56 per 100 000, 59 per 100 000, and 43 per 100 000 for the three age groups.

Table 3. Summary of Poisson regression analyses showing age- and sex-specific annual increases (95% confidence interval) expressed as percentage during 1989–2009

	Boys	Girls	Boys and girls
0–4 yr	6.4 (4.6–8.2)	6.0 (4.2–7.9)	6.2 (4.9–7.5)
5–9 yr	5.2 (3.8–6.6)	4.6 (3.2–6.0)	4.9 (3.9–5.9)
10–14 yr	4.5 (3.3–5.7)	1.9 (0.7–3.2)	3.3 (2.4–4.1)
All ages	5.1 (4.3–5.9)	3.7 (2.9–4.6)	4.4 (3.9–5.0)

Discussion

This study has reported the 21-yr data of the Hungarian Childhood Diabetes Registry during 1989–2009 in a genetically stable, homogenous population using standard criteria and method, with an ascertainment level of 95% over the years. With the overall incidence rate of 12.5 per 100 000 per yr, which is comparable with the incidence in the surrounding countries (6–9), Hungary belongs to the medium incidence geographical regions. During the observation period, the background population of children aged below 15 yr has dropped by a third, and at the same time the number of newly diagnosed children increased considerably by around 40 new cases per yr in boys and 20 new cases per yr in girls. These changes have resulted in the 2.4-fold increase in incidence of type 1 diabetes in Hungarian children during 1989–2009 exceeding the earlier prediction – based on the observed trend between 1989 and 1998 – of a doubling in incidence rates in 15 yr (10).

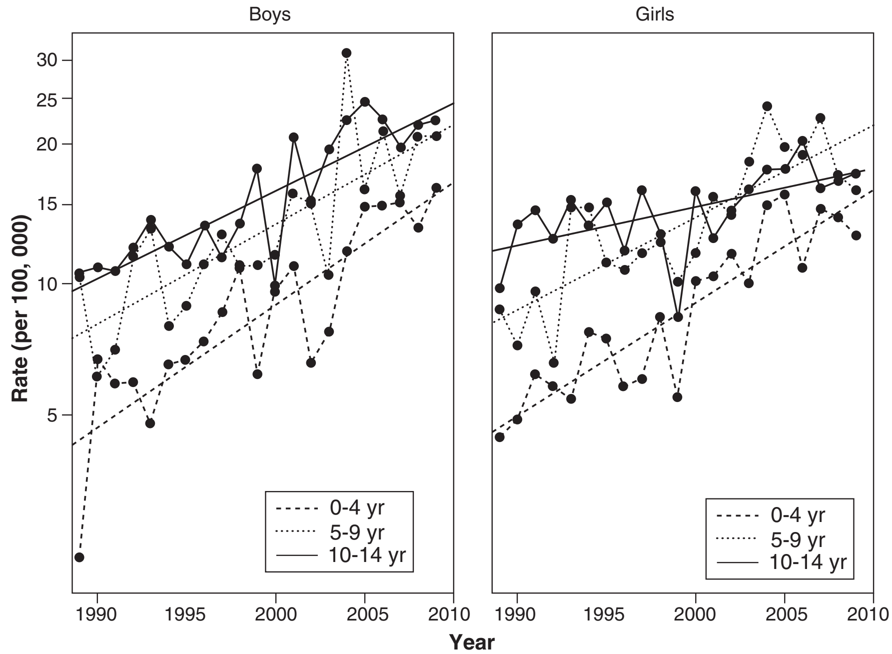

Fig. 2. Time trends in age-specific incidence rates in boys and girls plotted on a logarithmic scale for each year in the period 1989–2009.

The peak incidence rate still occurs in the 10–14-yr old age group as at the beginning of the study period but because of the rapid increase in younger children the difference in incidence among the age groups seems to be diminishing; the incidence among the 5–9-yr age group has now reached that of the 10–14-yr age group, particularly in females. In more recent years, a male excess in the age-standardized rate has become evident compared with a female excess noted previously, and the Poisson regression analysis detected this difference in rates of increase between the sexes (10).

The statistical analysis showed an overall increasing trend with little evidence of deviation from linearity. However, the year 2004 was an outlier with higher incidence than predicted compared with previous years and the subsequent periods, mainly because of the unexpectedly high number of new cases observed in the 5–9-yr-old males. We observed similar transient stabilization of incidence (at a lower level) between 1980 and 1984 (4). Some of the high risk countries have also shown no increase in incidence for brief periods over the last 20 yr (11, 12) . The latest report from Finland (13) shows strikingly stable rates between 1980 and 1987 with subsequent steep increase. Recent publications from neighboring Austria (8) and Croatia (7) have also reported transient periods of stabilization (1979–1989 and 1995–2000, respectively), although the general trend remained clearly upward. When we compared the first 10-yr period with the second 11 yr we found that the increase was larger during 1999–2009 (5.2% vs. 3.6% during 1989–1998) although the difference was not significant. Publications from the neighboring countries of Hungary as well as other European populations reported similar increasing trends in incidence with accelerated increase in recent years (7, 8, 14–16). Although we found no evidence of systematic departures from log-linear trends, in countries with high incidence where the rate of increase is less steep suggesting a leveling off compared with medium- or low-incidence regions, a log-linear trend may not always be appropriate (3, 11). Reports of stabilization of rates should therefore be interpreted with caution, particularly if they are based solely on visual impression of short-term changes in rates or on the fitting of smoothed nonlinear relationships that do not offer any significant improvement in model fit. The prevailing pattern seems to be one of continuing increase.

Many attempts have been made to explain the rising trend in incidence over the past decades and several studies indicated the role of lifestyle-related risk factors (environmental exposures) such as high calorie intake, rapid early growth, and rapid early weight gain (17–20). It is of considerable significance that a recent publication from Sweden reported a leveling off of incidence in birth cohorts from the year 2000 and thereafter (3) paralleling a decline in the prevalence of overweight and obesity in 4-yr-old children. It is at present too early to know whether or not this new observation is an isolated phenomenon unique to Sweden or if it will generalize to other populations in due course. However, the claim that this represents a shift back to older age at onset (3) seems premature until data are available on the risks in this young cohort at older age groups.

In conclusion, using the large database of a prospective registry covering about 75% of the total 0–14-yr-old population with high level of ascertainment of cases, we were able to study incidence trends with precise statistical methods over two decades. The most important finding of this study was that the annual increase (3.6%) of type 1 diabetes described previously has continued further at an even higher rate (5.3%) in the last 11 yr with no evidence of leveling off, although with a difference between the sexes primarily explained by the lower rate of increase in the 10–14-yr-old girls compared with boys. We anticipate that the long-term general trend will continue to be upward. Continued registration of incidence is of paramount importance to recognize long-term tendencies, which may provide clues to the environmental exposures behind these trends. Furthermore, appropriate planning of services and resources are necessary to meet the need for the increased number of children diagnosed with diabetes.

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References

1. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 2009: 373: 2027–2033.
2. Gale EA. Spring harvest? Reflections on the rise of type 1 diabetes. Diabetologia 2005: 48: 2445–2450.
3. Berhan Y, Waernbaum I, Lind T, Mollsten A, Dahlquist G. Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden. Diabetes 2011: 60: 577–581.
4. Soltesz G, Madacsy L, Bekefi D, Danko I. Rising incidence of type 1 diabetes in Hungarian children (1978-1987). Hungarian Childhood Diabetes Epidemiology Group. Diabetic Medicine 1990: 7: 111–114.
5. Bishop YM, Fienberg SE, Holland PW. Discrete Multivariate Analysis: Theory and Practice. Cambridge, MA: MIT Press, 1974.
6. Michalkova D, Minarik P, Hlava P, Camajova J, Nazarov V. Trends in the incidence of childhood-onset type 1 diabetes in Slovakia 1985-2000. Central European Journal of Public Health 2004: 12: 75–77.
7. Stipancic G, La Grasta Sabolic L, Malenica M, Radica A, Skrabic V, Tiljak MK. Incidence and trends of childhood type 1 diabetes in Croatia from 1995 to 2003. Diabetes Research and Clinical Practice 2008: 80: 122–127.
8. Schober E, Rami B, Waldhoer T. Steep increase of incidence of childhood diabetes since 1999 in Austria. Time trend analysis 1979-2005. A nationwide study. European Journal of Pediatrics 2008: 167: 293–297.
9. Bratina NU, Tahirovic H, Battelino T, Krzisnik C. Incidence of childhood-onset type I diabetes in Slovenia and the Tuzia region (Bosnia and Herzegovina) in the period 1990-1998. Diabetologia 2001: 44 (Suppl 3): B27–B31.
10. Gyurus E, Green A, Patterson CC, Soltesz G. Dynamic changes in the trends in incidence of type 1 diabetes in children in Hungary (1978-98). Pediatric Diabetes 2002: 3: 194–199.
11. Joner G, Stene LC, Sovik O. Nationwide, prospective registration of type 1 diabetes in children aged <15 years in Norway 1989-1998: no increase but significant regional variation in incidence. Diabetes Care 2004: 27: 1618–1622.
12. Taplin CE, Craig ME, Lloyd M et al. The rising incidence of childhood type 1 diabetes in New South Wales, 1990-2002. Medical Journal of Australia 2005: 183: 243–246.
13. Harjutsalo V, Sjoberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. Lancet 2008: 371: 1777–1782.
14. Ehehalt S, Blumenstock G, Willasch AM, Hub R, Ranke MB, Neu A. Continuous rise in incidence of childhood type 1 diabetes in Germany. Diabetic Medicine 2008: 25: 755–757.
15. Cinek O, Sumnik Z, Vavrinec J. Childhood diabetes in the Czech Republic: a steady increase in incidence. Casopis Lekaru Ceskych 2005: 144: 266–271; discussion 71–72.
16. Jarosz-Chobot P, Polanska J, Szadkowska A et al. Rapid increase in the incidence of type 1 diabetes in Polish children from 1989 to 2004, and predictions for 2010 to 2025. Diabetologia 2011: 54: 508–515.
17. Hypponen E, Virtanen SM, Kenward MG, Knip M, Akerblom HK. Obesity, increased linear growth, and risk of type 1 diabetes in children. Diabetes Care 2000: 23: 1755–1760.
18. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. Diabetologia 2001: 44: 914–922.
19. Knip M, Virtanen SM, Akerblom HK. Infant feeding and the risk of type 1 diabetes. American Journal of Clinical Nutrition 2010: 91: 1506S–1513S.
20. Dahlquist G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. Diabetologia 2006: 49: 20–24.